Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

CBER (b) (6) CMC/Facility BLA Review Memorandum

BLA STN 125817/0

Novavax COVID-19 Vaccine, Adjuvanted
Nuvaxovid

(b) (6)

(b) (6)

1. BLA#: STN 125817/0

2. APPPLICANT NAME AND LICENSE NUMBER
Novavax, Inc. (US License No. # 2349)

3. PRODUCT NAME/PRODUCT TYPE
Established Name: Novavax COVID-19 Vaccine, Adjuvanted
Proprietary Name: Nuvaxovid

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

a. Pharmaceutical Category: Vaccine
b. Dosage form: Dispersion
c. Strength/Potency: 5 mcg
d. Route of administration: Injection (Intramuscular)
e. Indication(s): Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

5. MAJOR MILESTONES

Milestones	Dates
Filing Rolling	Roll 1 - January 31, 2024 Roll 2 - February 29, 2024 Roll 3 - April 1, 2024
Filing Meeting	April 22, 2024
Mid-Cycle Communication	October 1, 2024
On-site Inspection	(b) (4)
Late-Cycle Meeting	December 15, 2024
PDUFA Action Due Date	April 1, 2025

6. (b) (6) CMC/FACILITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)

7. INTER-CENTER CONSULTS REQUESTED

N/A

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments
January 31, 2024	STN 125817/0.0	Roll 1 [a]
February 29, 2024	STN 125817/0.2	Roll 2 [b]
April 1, 2024	STN 125817/0.4	Roll 3 [c]
October 1, 2024	STN 125817/0.38	Response to IR dated September 20, 2024, regarding CCIT via (b) (4) on vial presentations
October 31, 2024	STN 125817/0.42	CMC information for 2024-2025 formula, JN.1 strain, in Pre-Filled Syringe (PFS) presentation
December 12, 2024	STN 125817/0.51	Response to email communication dated November 21, 2024, regarding shipping validations for drug product in PFS presentation
January 8, 2025	STN 125817/0.61	Response to IR dated September 20, 2024, regarding CCIT via (b) (4) method in (b) (4) study
January 30, 2025	STN 125817/0.67	Response to IR dated January 24, 2025, regarding Shipping Validation for the vaccine in PFS presentation
February 25, 2025	STN 125817/0.76	Response to CBER's advice and comments dated February 23, 2025, on Shipping Validation studies for Drug Product (DP) in PFS presentation
February 27, 2025	STN 125817/0.78	Response to CBER's comments (follow-up) dated February 26, 2025, regarding Shipping Validation studies for DP in PFS presentation
March 17, 2025	STN 125817/0.92	Response to the Post-Marketing Commitment communication dated March 14, 2025,

a. Roll 1 included the following information: (1) (b) (4) for Wuhan strain 5 Dose Vial (DV) and 10 DV; (2) Facility information of SIIPL (Drug Substance and Drug Product manufacturing site); (3) Quality information for Matrix-A and Matrix-C manufactured in facilities of AGC-CPH and Novavax AB.
b. Roll 2 included nonclinical information (not under (b) (6) purview).
c. Roll 3 included the following information: (1) (b) (4) for XBB.1.5 strain – 5 DV; (2) Drug Product for Wuhan strain 5 DV & 10 DV, and XBB.1.5 strain 5 DV.

9. REFERENCED REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type	Holder	Referenced Item	Letter of Cross-Reference	Comments
IND 22430	Novavax Inc.	Novavax COVID-19 Vaccine, Adjuvanted	N/A	
EUA 28237	Novavax Inc.	Novavax COVID-19 Vaccine, Adjuvanted	N/A	
DMF (b) (4)	(b) (4)	(b) (4)	Yes	Defer to OVRR
DMF (b) (4)	(b) (4))	Glass Prefilled Syringe (PFS)	Yes	
Device Master File (MAF) (b) (4)	(b) (4)	SARS-CoV-2 Neutralizing Antibody Assay	Yes	Defer to OVRR
Master File (b) (4)	(b) (4)	Drug Product Testing	Yes	Defer to OVRR

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Novavax Inc. (Novavax) submitted the BLA STN 125817/0.0 in rolling with part one provided on January 31, 2024, to support the licensure application for Nuvaxovid [Novavax COVID-19 Vaccine, Adjuvanted]. The Nuvaxovid drug product (DP) consists of SARS CoV-2 (severe acute respiratory syndrome coronavirus 2) recombinant spike protein of variants (Wuhan, XBB.1.5 or JN.1), adjuvanted with Matrix-M adjuvant, and packaged in a multidose vial or prefilled syringe (PFS) as protein nanoparticles in dispersion for intramuscular injection. Adjuvant Matrix-M is derived from *Quillaja saponaria* saponins, Fraction-A and Fraction-C. Nuvaxovid is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS CoV-2 in individuals 12 years of age and older.

Multiple facilities involve the manufacture of Nuvaxovid, including drug substance (DS) manufactured at Serum Institute of India Pvt. Ltd. (SIIPL) Manjari; the DS Adjuvant components, Matrix-A and Matrix-C, manufactured at Novavax AB, Uppsala, Sweden (NVX-AB), AGC Biologics A/S, Copenhagen, Denmark (AGC-CPH), (b) (4) DP manufactured at SIIPL (b) (4) for presentations of 10-dose vial (10 DV), 5-dose vial (5 DV), and PFS for the COVID19 variants Wuhan, XBB.1.5 and JN.1. The manufacturing data provided in the BLA includes Wuhan strain in 10 DV and 5 DV presentations, XBB.1.5 in 5 DV presentation and JN.1 in PFS presentation. The testing facilities for DS, DP, intermediates, and the adjuvants during Nuvaxovid manufacture are detailed in the facility table (3.2.A.1) in the memo.

CBER(b) (6) reviewed the DS and DP manufacturing processes, equipment and facilities proposed for manufacture of Nuvaxovid. Information reviewed and documented in this memo includes data to validate and support the consistency of the manufacturing process and product quality, information of facility and utility, measures of cross-contamination prevention, aseptic operations, maintenance of controlled environments, and equipment for use in the manufacturing including types of usage (i.e., dedicated, or shared, multi-use or single-use) and qualification, cleaning, and sterilization.

The pre-licensing inspection (PLI) for the SIIPL (b) (4) facility was performed jointly by (b) (6) Office of Vaccine Research and Review (OVRR) and (b) (6) from (b) (4) . A five-item FDA Form 483 was issued to SIIPL at the closing of the PLI.

11. RECOMMENDATION

I. APPROVAL

(b) (6) recommends approval of this BLA, STN 125817/0, to manufacture Nuvaxovid drug substance (DS) and drug product (DP) at Serum Institute of India Pvt. Ltd. located in (b) (4)

The applicant committed to submit a final report of Shipping Validation study for Nuvaxovid in pre-filled syringe presentation as a Post-Marketing Commitment (PMC) submission by July 31, 2025 (PMC#1). The PMC includes one item as follows:

1. Please repeat the shipping validation study with a minimum of (b) (4) commercial lots of the JN.1 DP in PFS presentation.
    a. The study should be initiated with recently manufactured DP lots and the relative potency of the shipped samples should be comparable to the relative potency at release.
    b. Please ensure that you include valid container closure integrity testing (CCIT) and sterility testing in your repeat shipping validation study to demonstrate your ability to maintain integrity/sterility for DP in the selected packaging configuration(s) and shipping route(s).

II. COMPLETE RESPONSE (CR)

N/A

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
(b) (6)	Concur	
(b) (6)	Concur	
(b) (6)	Concur	

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Module 3

The submission STN 125817/0 contains five modules of Drug Substance (DS), three modules of Drug Product (DP) and six sets of Facility and Equipment sections for the Novavax COVID19 Vaccine multi-dose vial and prefilled syringe presentations. These modules are listed below:

DS Modules
- 3.2.S DS [SARS-CoV-2 rS] [SIIPL] *for Wuhan strain*
- 3.2.S DS [SARS-CoV-2 rS, Variant] [ALL] *for XBB.1.5 strain*
- 3.2.S DS [SARS-CoV-2 rS, JN.1] [ALL] *for JN.1 strain*
- 3.2.S DS [Matrix-A & Matrix-C] [NVX-AB]
- 3.2.S DS [Matrix-A & Matrix-C] [AGC-CPG]

DP Modules
- 3.2.P DP [SARS-CoV-2 rS Vaccine, Adjuvanted, Prototype] *for Wuhan strain*
- 3.2.P DP [SARS-CoV-2 rS Vaccine, Adjuvanted, Variant] *for XBB.1.5 strain*
- 3.2.P DP [SARS-CoV-2 rS Vaccine, Adjuvanted, JN.1] *for JN.1 strain*

Facility and Equipment Sections
- Facilities and Equipment_SIIPL
- Facilities and Equipment_620PD
- Facilities and Equipment_NVX AB
- Facilities and Equipment_AGC-CPH
- Facilities and Equipment_(b) (4)
- Facilities and Equipment_(b) (4)

The information of Chemistry, Manufacture and Control (CMC), including facility / equipment and device for the 2024-2025 strain, JN.1, in Pre-Filled Syringe (PFS) presentation (JN.1 PFS) was provided in amendment STN 125817/0.42 (October 30, 2024). The vast majority of the information for JN.1 PFS remained identical to the information that was reviewed under Emergency Use Authorization (EUA) 28237/0.246 (b) (6) August 30, 2024). This memo focuses on the updated information in comparison to EUA 28237/0.246 regarding the JN.1 PFS vaccine.

The modules identified above are reviewed under consolidated sections of DS, DP, Facility / Equipment and Regional (Device) in this memo.

3.2.S DRUG SUBSTANCE [SARS-CoV-2 rS]

This section covered the following modules submitted in the BLA:
- 3.2.S DS [SARS-CoV-2 rS] [SIIPL] *for Wuhan strain* (STN 125817/0.0)
- 3.2.S DS [SARS-CoV-2 rS, Variant] [ALL] *for XBB.1.5 strain* (STN 125817/0.0)

- 3.2.S DS [SARS-CoV-2 rS, JN.1] [ALL] *for JN.1 strain* (STN 125817/0.42)

3.2.S.1 GENERAL INFORMATION

The name of Drug Substance (DS) is SARS-CoV-2 rS DS Wuhan, XBB.1.5 or JN.1.

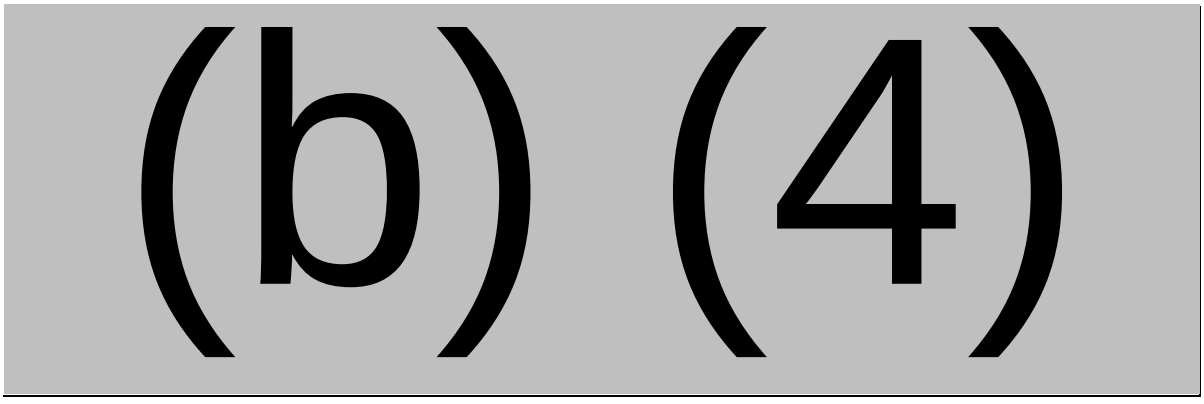
We defer review of the structure and general properties of DS to the Office of Vaccines Research and Review (OVRR).

3.2.S.2 Manufacture
3.2.S.2.1 Manufacturer(s)

See section 3.2.A.1 for a complete list of drug substance manufacturers.

3.2.S.2.2 Description of Manufacturing Process

(b) (4)



11 pages determined to be not releasable: (b)(4)

(b) (4)

3.2.P DRUG PRODUCT

This section of the review memo covered the following submissions:

- 3.2.P DP [SARS-CoV-2 rS Vaccine, Adjuvanted, Prototype] *for Wuhan strain* (STN 125817/0.0)
- 3.2.P DP [SARS-CoV-2 rS Vaccine, Adjuvanted, Variant] *for XBB.1.5 strain* (STN 125817/0.0)
- 3.2.P DP [SARS-CoV-2 rS Vaccine, Adjuvanted, JN.1] *for JN.1 strain* (STN 125817/0.42)

3.2.P.1 Description and Composition of the Drug Product

Novavax COVID-19 Vaccine, dispersion for injection, is a recombinant spike protein vaccine. It is a sterile, preservative-free, aqueous buffered dispersion of the SARS-CoV-2 rS protein that is co-formulated with Matrix-M1 adjuvant and presented in a multi-dose vial containing five or ten doses (5-Dose Vial, 5DV or 10-Dose Vial, 10DV) or a prefilled syringe (PFS).

A single human dose of DP is 0.5 mL. The storage condition of DP is 2-8 °C.

3.2.P.2.4 Container Closure System

Container Closure Integrity Testing (CCIT)
CCIT is tested in DP stability study (but not at release) for the Novavax COVID-19 Vaccine in both multi-dose vial and PFS presentations. CCIT validation on filled vials was performed on-site using (b) (4) method. CCIT validation on PFS product was performed by a 3rd party CMO, (b) (4).

The initial CCIT validation for DP in vials was performed in 2019 using (b) (4)

Reviewer's Comments*: The original CCIT validation for the Novavax COVID19 Vaccine products was assessed as inadequate based on the following:*

- (b) (4)

(b) (4)

IR was issued on September 20, 2024, regarding the described concerns on CCIT. Novavax replied on October 1, 2024 (STN 125817/0.38) with a CCIT validation report MMSR-0475-000 (effective on May 27, 2024) as follows:

- (b) (4)

***Reviewer's Comments**: The data from the IR response appears to support that* (b) (4) *However, the overall IR response of CCIT validation using* (b) (4) *method still appeared insufficient on the following:*

- (b) (4)

  .

The firm described in the original submission that CCIT for simulated vials in (b) (4) *studies was performed using* (b) (4) *method. CCIT validation via* (b) (4) *method was provided upon an information request (IR) as described below.*

Novavax reported in the original Aseptic Process Simulation (APS) study that filled vials after (b) (4) were tested for CCIT via (b) (4) Method. IR was issued on September 20, 2024 for CCIT validation report using (b) (4) method for the vial product. In response to the IR, a validation procedure (SOP m-ex-tm-00816) of CCIT via (b) (4) for the vaccine in vial presentation was provided in STN 125817/0.38, and the validation report of CCIT via (b) (4) was provided in STN 125817/0.61 (QAG_30477). A summary of CCIT validation using (b) (4) is as follows:

- (b) (4)

Reviewer's Comments*: The provided IR response supported a limit of detection at* (b) (4) *for CCIT via* (b) (4) *method for the COVID-19 product in vial*

presentations. The results of no growth on test samples supported the container closure integrity for DP vials manufactured from the filling line in SIIPL. The overall information of CCIT via (b) (4) *method for DP in vial presentation appears acceptable.*

The information provided in this section of CCIT validation using (b) (4) *method demonstrated that the vial product(s) manufactured from the same vial filling line in SIIPL was able to maintain integrity for the vial product(s) in final packaging configuration, therefore, the concerns of CCIT validation for the vaccine in vial presentation is resolved.*

CCIT on Novavax COVID19 vaccine in PFS presentation was evaluated as acceptable during the authorization of EUA 28237/0.246 (August 30, 2024).

In-Use Stability Study for DP in Multi-Dose Vials

The in-use stability of the multidose vials after multiple withdrawals was provided in the following reports (STN 125817/0.4):

- (b) (4)

The testing vials were challenged (b) (4) times (for 5 DV) or (b) (4) times (for 10 DV) for injection withdrawal and puncture using syringes through the stoppers. After (b) (4), the vials were (b) (4). Endotoxin and sterility were tested at the (b) (4) (to mimic the last withdrawal for the 5 DV or 10 DV products) for the challenged vials. Testing results for both Sterility (no evidence of microbial growth) and Endotoxin (b) (4)) met predefined acceptance criteria.

Reviewer's Comments*: Testing vials were challenged to mimic the entire* (b) (4) *withdrawal for the 5 DV or 10 DV products. The in-use shelf-life for the multi-dose vials is proposed for* (b) (4) *. The stability results supported the sterility assurance of the 5 DV and 10 DV products during their clinical usage with multiple withdrawals. The provided information appears acceptable from* (b) (6) *perspective.*

3.2.P.2.5 Microbiological Attributes

The vials used for the COVID-19 Vaccine in vial presentation are depyrogenated by (b) (4). Stoppers and seals are sterilized by steam sterilization in a closure processing system.

Reviewer's Comments*: Identical data for microbial attributes and controls for the PFS were reviewed and found acceptable in EUA 28237/0.246 (August 30, 2024).*

3.2.P.3 Manufacture
3.2.P.3.1 Manufacturer(s)

Refer to section 3.2.A.1 for a complete list of all manufacturing facilities.

3.2.P.3.3 Description of Manufacturing Process

The Novavax COVID-19 Vaccine, dispersion for injection, DP (Wuhan – 5 DV and 10 DV; XBB.1.5 – 5 DV) is manufactured in (b) (4)

The DP manufacturing steps include the following:

- (b) (4)

The critical process parameters and in-process controls under (b) (6) purview include the follows:

- (b) (4)

(b) (4)

No reprocessing occurs during any stage of drug product manufacture.

***Reviewer's Comment**: This overall information of manufacturing processes and controls for Novavax COVID19 Vaccine in vial presentations (Wuhan – 5 DV and 10 DV; XBB.1.5 – 5 DV) appears acceptable. Visual inspection of the filled vials for the COVID19 vaccine was inspected during CBER's 2024 on-site inspection in SIIPL, with no objectional findings noted.*

The information of Description of Manufacturing Process for JN.1 PFS vaccine was submitted in STN 125817/0.42. The content for JN.1 PFS remains the same as what has been reviewed during authorization in EUA 28237/0.246.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The following process parameters were provided regarding the processes of sterilization of filling machine parts, rubber stoppers and aluminum seals, washing of vials, depyrogenation of vials, and sterile filtration:

(b) (4)

***Reviewer's Comment**: The validation of sterile filtration is described in module 3.2.P.3.5 in this memo. The validations of* (b) (4) *sterilization, depyrogenation and equipment cleaning are described in module 3.2.A.1 [SIIPL] in this memo.*

The provided information of Controls of Critical Steps and Intermediates for JN.1 PFS remains the same as what has been authorized in EUA 28237/0.246.

3.2.P.3.5 Process Validation and/or Evaluation

Process Validation of Novavax COVID-19 Vaccine in Multi-dose Vial Presentation

The following DP PPQ batches were manufactured of Process Validation for the vaccine in multi-dose vial presentation:

- (b) (4)

(b) (4)

5 pages determined to be not releasable: (b)(4)

- (b) (4)



3.2.P.5 Control of Drug Product
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

The DP specification at release and to the end of shelf-life for the Novavax COVID-19 Vaccine, in multi-dose vial presentation are as follows (under (b) (6) purview, STN 125817/0.5):

Test Method	Compendial Reference(s)	Release Acceptance Criteria	Stability Acceptance Criteria
Sterility by (b) (4)	(b) (4)	No growth	No growth
Endotoxin by (b) (4)	(b) (4)	(b) (4)	NA
Container Closure Integrity Test (CCIT)	(b) (4)	Not Applicable	(b) (4)

The DP specification at release and over shelf-life for the Novavax COVID-19 Vaccine, in PFS presentation are as follows (STN 125817/0.42):

Test Method	Compendial Reference(s)	Release Acceptance Criteria	Stability Acceptance Criteria
Sterility by (b) (4)	(b) (4)	No growth	No growth
Endotoxin by (b) (4))	(b) (4)	(b) (4)	NA

Test Method	Compendial Reference(s)	Release Acceptance Criteria	Stability Acceptance Criteria
Container Closure Integrity Test (CCIT)	(b) (4)	Not Applicable	No failures allowed
(b) (4)	(b) (4)	NA	(b) (4)

***Reviewer's Comment**: These provided DP specification appears acceptable.*

3.2.P.5.4 Batch Analyses

Novavax provided batch analysis results for the following batches:

(b) (4)

All tests on endotoxin and sterility at release met predefined acceptance criteria for the reported DP lots.

***Reviewer's Comments**: The provided batch analysis results for Novavax COVID19 vaccine, in both multi-dose vial and PFS presentations appear acceptable.*

3.2.P.7 Container Closure System

The primary container closure components for Novavax COVID-19 Vaccine in multi-dose vials are as follows (STN 125817/0.5):

Container Closure Component	Description	Supplier
Glass Vials	5 mL Clear, Tubular, (b) (4) type (b) (4) Glass Vials, siliconized	(b) (4)
Rubber Stoppers	13 mm Bromobutyl Ready for Sterilization (RFS) Rubber Stoppers, uncoated, siliconized	(b) (4)
Aluminum Flip-off seals	13 mm Aluminum Seal with blue plastic flip-off cap	(b) (4)

The drawings of the vial, stopper and flip-off aluminum seal were provided (Figures 1 - 3, module 3.2.P.7, STN 125817/0.5).

Novavax provided receiving QC testing results and suppliers' CoAs for the following CCS components - (b) (4) batches of 5 mL glass vials (Batches (b) (4) (b) (4) batch of flip-off aluminum seal (Batch No. (b) (4) and (b) (4) batch of 13 mm Bromobutyl RFS rubber stoppers (Batch No. (b) (4) The following tests are under (b) (6) purview:

- Incoming QC testing on 5 mL glass vials evaluated of description, visual inspection, average (b) (4) dimensions.
- Incoming QC testing on 13mm rubber stoppers evaluated of description, visual inspection, color shade, effect of (b) (4) or any visual change, endotoxin (action limit: (b) (4) /unit), bioburden (action limit: (b) (4) /unit), dimensions, and functionalities ((b) (4) .
- Incoming QC testing on flip-off aluminum seal evaluated of description, visual inspection, color shade, effect of (b) (4) (no change in color and (b) (4) and dimensions.

All results met predefined acceptance criteria for the incoming test on reported lots of 5 mL vials, rubber stopper and aluminum seals (b) (4) .

***Reviewer's Comments**: The same 5 mL type (b) (4) glass vial supplied from (b) (4) is used for filling both 5 DV (fill target (b) (4)) and 10 DV (fill target 6.1 mL) vaccines' production in SIIPL. Based on (b) (4) Glass Injection Vials specifications, the 5 mL vial holds a filling volume of more than (b) (4) mL (b) (4) The information of container closure system for multi-dose vials and the incoming tests for the CCS appear acceptable.*

The primary container closure components for Novavax COVID-19 Vaccine DP in PFS presentation are as follows (STN 125817/0.42):

Components	Description	Supplier
Glass Syringe	1 mL Standard, Round Flange, Siliconized Type (b) (4) borosilicate glass syringe barrel with Luer lock and Plastic Rigid Tip Cap with (b) (4) Elastomer, sterile, ready to use	(b) (4)

Components	Description	Supplier
Plunger Stopper	(b) (4)	(b) (4)

The supplier's Certificates of Analysis (CoA) and Certificate of Conformance (CoC) for the 1 mL glass syringe barrel with the plastic rigid tip cap and the plunger stopper was provided (STN 125817/0.42). Both components were supplied sterile and tested of sterility (acceptance criteria: Sterile) and endotoxin (b) (4) Testing results met predefined acceptance criteria in the provided CoCs.

***Reviewer's Comments**: The CCS information remains the same between EUA 28237/0.246 and STN 125817/0.42. The Container closure information for JN.1 PFS vaccine was reviewed and found acceptable during review of EUA 28237/0.246.*

3.2.P.8 Stability
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

Stability study under (b) (6) purview for the Novavax COVID-19 Vaccine in multi-dose vials was planned as follows (STN 125817/0.0):

Stability Study for Wuhan or XBB.1.5 in Multi-Dose Vial Presentation

Tests	Acceptance Criteria	Scheduled Stability Sampling Intervals
Sterility by (b) (4)	No evidence of microbial growth should be found	0, 6 (b) (4) months for long-term condition 5 ± 3 °C. 0 and 6 months for accelerated condition (b) (4) (b) (4) .
CCIT#	(b) (4)	0, 6, (b) (4) months for long-term condition 5 ± 3 °C. 0 and 6 months for accelerated condition (b) (4) (b) (4) .

 # For the XBB.1.5 – 5 DV DP batches manufactured in 2023 ((b) (4) series), long-term stability tests are scheduled to 24 months.

Stability Study of PPQ JN.1 PFS Presentation

Tests	Acceptance Criteria	Scheduled Stability Sampling Intervals
Sterility by (b) (4)	No Growth	0, (b) (4) months for long-term condition. 0 (b) (4) months for accelerated condition.
(b) (4)	(b) (4)	0, 3, (b) (4) months for long-term condition. 0, 3 (b) (4) months for accelerated condition.
CCIT	No Failure allowed	0, 3, (b) (4) months for long-term condition. 0, 3 (b) (4) months for accelerated condition.

Stability data were provided for the following:

- Wuhan – 5 DV Batches No. (b) (4) months' long-term & 6 months' accelerated stability data.
- Wuhan – 10 DV Batches No. (b) (4) months' long-term & 6 months' accelerated stability data.

- XBB.1.5 – 5 DV Batches No. (b) (4) – up to 6 months' long-term & initial to 1 month of accelerated stability data were reported.
- XBB.1.5 – PFS (b) (4) µg/mL) Batches No. (b) (4) months' long-term and 3 month's accelerated stability data were reported. Note – prior to manufacture of JN.1 PFS, Novavax manufactured XBB.1.5 PFS (IND 22430/627, April 12, 2024) and these XBB.1.5 PFS batches were included into stability program, which was intended to be used to leverage shelf-life for JN.1 PFS vaccine.
- JN.1 – PFS (b) (4) µg/mL) Batches No. (b) (4) – 3 months' long-term stability data and 3 months' accelerated stability data.
- JN.1 – PFS (b) (4) µg/mL) Batches No. (b) (4) – 3 months' long-term stability data & initial to 2 months' accelerated stability data; Batches No. (b) (4) – 2 months' long-term stability data; Batches (b) (4) – 1 month's long-term stability data.

All reported results on sterility (No Growth), CCIT (No Failures Allowed) and (b) (4) met predefined acceptance criteria.

The proposed shelf lives for Novavax COVID-19 Vaccines were as follows:

- A shelf life of (b) (4) at 2 – 8ºC for the Novavax COVID-19 Vaccine, Wuhan – 5 DV and 10 DV products.
- A shelf life of 9M at 2 – 8ºC for the Novavax COVID-19 Vaccine, XBB.1.5 – 5 DV product.
- An initial shelf life of 3M at 5 ± 3°C is proposed for Novavax COVID-19 Vaccine, JN.1 - PFS product.

Stability will continue to be monitored per the firm's stability protocols (3.2.P.8.1, STN 125817/0.4 & STN 125817/0.42).

> ***Reviewer's Comments****: Testing results on sterility, CCIT and* (b) (4) *met predefined acceptance criteria for the reported batches. The acceptability of the proposed shelf lives for the vaccines are deferred to OVRR.*

3.2.A.1 FACILITIES & EQUIPMENT [SIIPL]

This section covered the following submissions on Facilities & Equipment:

- 3.2.A.1 Facility and Equipment *for Wuhan and XBB.1.5 strains* (STN 125817/0.0)
- 3.2.A.1 Facility and Equipment [All] [SARS-CoV-2 rS, JN.1] *for JN.1 strain* (STN 125817/0.42)

All the facilities involved in the manufacture and testing of Novavax COVID-19 Vaccine, in multi-dose vial (10 DV & 5 DV) and PFS, are listed in the Facility Table below.

Novavax COVID19 Vaccine, Dispersion for Injection, (Wuhan – 5DV and 10 DV, XBB.1.5 - 10DV & JN.1 PFS) Manufacturing and Testing Facilities

No.	Facility	Operations	Inspection Status / Comments	Inspection/ Waiver
1	**Serum Institute of India Pvt. Ltd.** (b) (4) India (b) (4) (SIIPL (b) (4)	Historical Site of Preparation and Testing of (b) (4) and Storage of (b) (4) (SIIPL (b) (4)). **DS** - Manufacturing, Storage, Primary and Secondary Packaging, and Distribution; QC Release, Stability, and In Process Testing. Preparation of (b) (4), Storage of (b) (4), and Testing of (b) (4). **DP** - Manufacturing, Labeling and Packaging; QC Batch Release, Stability and In Process Testing.	On-site inspection by CBER / (b) (6) on (b) (4) regarding the Novavax COVID vaccine (SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine with Matrix-M Adjuvant). Inspection outcome was VAI. ***Note-*** *The SIIPL* (b) (4) *SIIPL* (b) (4) *SIIPL* (b) (4)	On-site inspection, (b) (4) VAI
2	(b) (4)	Testing of (b) (4) In Process Testing for DS (b) (4)	Surveillance Inspection, (b) (6) (b) (6), (b) (4). NAI.	Not required
3	(b) (4)	Testing of (b) (4) Manufacture of (b) (4) In Process Testing for DS (b) (4)	Surveillance Inspection, (b) (6) (b) (6) (b) (4). NAI.	Not required
4	**Novavax Inc. –** (b) (4)	In-Process testing of DS (quantitation (b) (4)	No FDA Inspection History	Not required
5	(b) (4)	In-Process testing for DS (b) (4))	Surveillance Inspection,(b) (6), (b) (4) NAI.	Not required

No.	Facility	Operations	Inspection Status / Comments	Inspection/ Waiver
6	**Novavax Inc.** 620 Professional Drive, Gaithersburg, MD. 20879 (b) (4)	Manufacture of (b) (4)	No FDA Inspection History	Not required
7	**Novavax CZ.** (b) (4)	Testing of (b) (4)	No FDA Inspection History	Not required
8	**Novavax AB** (b) (4)	**DP-** QC Batch Release and Stability testing (Particle size; Matrix-A/C contents)	No Prior FDA Inspection History. Inspected by (b) (4) Acceptable GMP Certificate issued.	Waived
9	(b) (4)	**DS-** QC Release and Stability Testing (Identity by (b) (4)) **DP-** QC Batch Release and Stability (Identity by (b) (4)	No prior FDA inspection History. Inspected by (b) (4) . Acceptable GMP Certificate issued.	Waived
10	(b) (4)	Storage of (b) (4)	Abbreviated Inspection by (b) (6), (b) (4) NAI.	Not required
11	**Facility**: **Fisher** (b) (4)	**DS:** Storage of (b) (4)	Abbreviated inspection by (b) (6) on (b) (4) NAI.	Not Required
12	(b) (4)	**DP:** QC release testing (expelled volume) and stability testing (CCIT, (b) (4) for JN.1 PFS	Surveillance inspection, (b) (6), (b) (4) NAI.	Waived

Abbreviations: CCIT: Container Closure Integrity Test; (b) (6) *DS: Drug Substance; DP: Drug Product; EUA: Emergency Use Authorization; FDA: Food & Drug Administration; FEI: FDA Establishment Identifier; GMP: Good Manufacturing Practice;* (b) (4) *NAI: No Action Indicated;* (b) (6) *QC: Quality Control; SIIPL: Serum Institute of India Pvt. Ltd. India; VAI: Voluntary Action Indicated; SARS-CoV-2 rS: SARS-CoV-2 Recombinant Spike Protein;* (b) (4) .

I. Facility Overview of SIIPL

(b) (4)

(b) (4)

(b) (4)

2 pages determined to be not releasable: (b)(4)

- (b) (4)

III. Environmental Monitoring

The information for EMPQ and location selection / monitoring frequency / acceptance criteria in routine EM for the COIVD-19 vaccine manufacture is identical to the data reviewed and found acceptable in EUA 28237/0.246 (August 30, 2024).

(b) (4)

IV. Equipment

Equipment used for Novavax COVID19 Vaccines, multi-dose vials, DS and DP manufacture were provided as follows:

(b) (4)

(b) (4)

(b) (4)

5 pages determined to be not releasable: (b)(4)

(b) (4)

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V. Disinfectant Efficacy Studies

***Reviewer's Comment**: Data for Disinfectant Efficacy Studies (DES) was not provided in the BLA. Summary Reports for DES validation study performed in September 2022 – January 2023 (QAG-28386/7/8/9, IND 22430/641) for SIIPL facility was reviewed and found acceptable in EUA 28237/0.246* (b) (6) *August 30, 2024). DES study for the COVID19 vaccine manufacture in SIIPL was reviewed and found acceptable in the* (b) (4) *PLI (*(b) (6) *).*

VI. Utilities

(b) (4)

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VII. Computerized Systems

The information provided for the computerized systems used for manufacture of Novavax COVID19 Vaccines in both multi-dose vial and PFS presentations was consistent with the contents reviewed in EUA 28237/0.246.

VIII. Contamination Prevention and Cross-contamination Controls

The information of contamination prevention and cross-contamination controls was consistent with information in EUA 28237/0.246; data was reviewed and found acceptable.

3.2.A.1 FACILITIES & EQUIPMENT [620PD]

Novavax, Inc. located at 620 Professional Drive, Gaithersburg, MD (620PD) [FEI: 30188665537] is responsible for preparation of (b) (4) for Nuvaxvoid product. 620PD only performs production using the Novavax (b) (4) platform. The facility is a single floor comprising areas of process development, manufacturing, and storage (STN 125817/0.42).

A summary of facility information and operational controls for the 620 facility:

- (b) (4)

The 620PD facility has an EM program in place monitoring viable (air & surface) microorganisms and non-viable particles (b) (4) using (b) (4) . The frequencies and locations of the routine EM were selected based on area classification and EMPQ results. The alert and action limits were defined per (b) (4) .

All product-contact equipment (b) (4) are single-use. A (b) (4) system is utilized for

open operations such as [redacted] in operations. The (b) (4) is equipped with an integrated (b) (4) decontamination system. (b) (4) decontamination of the [redacted] is performed (b) (4) [redacted] - use. The (b) (4) is requalified every (b) (4) [redacted] per procedure. The site also has storage for room temperature, cold storage (2 – 8°C, (b) (4) [redacted] and (b) (4) [redacted]

Written procedures of facility sanitization are in place. DES study has been performed and disinfectants were qualified for facility sanitization usage. Room cleaning, including ceiling, walls, floors, and doors, is performed during the (b) (4) [redacted] process.

Materials of (b) (4) [redacted] and single-use consumables are purchased ready-to-use (pre-sterilized) and released against approved specifications. (b) (4) [redacted] are steam sterilized in a qualified (b) (4) [redacted]. The materials are (b) (4) [redacted] as they are introduced into manufacturing rooms.

The site has clean steam and Clean Compressed Air (CCA) that are generated on-site. Clean steam generated from (b) (4) [redacted] water is used for autoclave sterilization. The clean steam generator was qualified, and the clean steam was consecutively sampled and tested under a performance qualification protocol prior to being released for manufacture. The clean steam is routinely sampled and tested for (b) (4) [redacted] via QC Monitoring Program.

CCA is generated by (b) (4) [redacted] to being distributed to POUs in GMP area. CCA is routinely monitored fo (b) (4) [redacted] The site also has (b) (4) [redacted] as a back-up for GMP usage.

Computerized systems used in 620PD facility include (b) (4) [redacted] (monitoring temperature, humidity, and differential pressure), (b) (4) [redacted] (Laboratory Information Management System), (b) (4) [redacted] (material and logistics) and (b) (4) [redacted] (Electronic Document Management). These computerized systems were validated per internal computer system validation procedures and managed in periodic reviews.

> ***Reviewer's Comments****: The 620PD facility functions to manufacture* (b) (4) [redacted] *of Novavax COVID19 Vaccine manufacture (Note- the* (b) (4) [redacted] *is derived from* (b) (4) *and manufactured in SIIPL). Novavax has established specifications for* (b) (4)*. Upon preparation, the* (b) (4) *is tested against existing specification, including sterility per* (b) (4) [redacted] *as well as* (b) (4) [redacted] *by* (b) (4)*. The testing results on microbial/sterility attributes for the* (b) (4) *batches of* (b) (4) *used in PPQ manufacture met predefined acceptance criteria (3.2.S.2.3, STN 125817/0.0). The* (b) (4) *manufactured from 620PD is quality control tested at release per predefined specifications. The overall information provided regarding facility and equipment for the 620PD facility appeared to be acceptable to support processing of* (b) (4) *,*

(b) (4)

3.2.A.1 FACILITIES & EQUIPMENT [Matrix-A & Matrix-C]

This section covers the following Facility and Equipment information submitted in STN 125817/0.0:

- Facilities and Equipment_NVX AB
- Facilities and Equipment_AGC-CPH
- Facilities and Equipment_(b) (4)
- Facilities and Equipment_(b) (4)

The manufacturers and QC testing facilities for the Matrix-A and Matrix-C components are as follows:

No.	Facility	Operations	Inspection Status / Comments	Inspection / Waiver
1	**Novavax AB (NVX AB) *** (b) (4), Uppsala, Sweden (b) (4)	Manufacture, QC In-Process, Release, and Stability Testing, Labeling, Packaging, and Storage of Matrix-A and Matrix-C. *Novavax AB is also a DP QC Batch Release and Stability testing site	No FDA inspection history in OSAR. GMP certificate issued by (b) (4) for an inspection performed on (b) (4) Inspection report obtained via (b) (4) for evaluation to support the waiver.	Waiver (due to being a DP QC testing site)
2	(b) (4)	Raw Material and Release Testing of Matrix A & Matrix C (b) (4) Filling of Matrix A & Matrix C	Surveillance inspection by (b) (6) on (b) (4) NAI	Not required
3	(b) (4)	QC Testing for Raw Materials	Surveillance inspection by (b) (6) on (b) (4) VAI	Not required

No.	Facility	Operations	Inspection Status / Comments	Inspection / Waiver
4	(b) (4)	(b) (4) Filling, Labeling, Packaging and Storage of Matrix-A and Matrix-C	----	Not required
5	**AGC Biologics A/S (AGC-CPH)** (b) (4)	Manufacture, (b) (4) and Filling, In Process and Release Testing, Labeling, Packaging and Storage of Matrix-A and Matrix-C. QC Testing of Raw Materials	Surveillance inspection by (b) (4). VAI. Compliance inspection by CDER on (b) (4). VAI CDER has an ongoing inspection with the site.	Not required
6	(b) (4)	QC Testing of Raw Materials for Matrix (-A or -C) manufactured in AGC-CPH	Surveillance inspection by (b) (6) on (b) (4). NAI	Not required

Facility and Equipment NVX AB

Novavax AB (NVX AB) in Uppsala, Sweden (b) (4) is wholly owned by Novavax Inc. (USA). Novavax AB is a facility dedicated to the production of the Matrix (-A or -C) at (b) (4) scales as well as the Matrix-M1 and Matrix-V. The site has (b) (4) production unit (b) (4) including (b) (4) manufacturing lines (each with a (b) (4) capacity) and a QC laboratory on the (b) (4) floor of the same building. The (b) (4) Matrix is shipped to (b) (4) (Uppsala, Sweden) (b) (4) Matrix (-A or -C).

The cleanrooms used to produce the Matrix (-A or -C) are classified as Grade (b) (4) consisting of (b) (4) The operation of formulation is an (b) (4) are closed in the facility.

Air is supplied to Grade (b) (4) manufacturing room through (b) (4). Fresh air is supplied from (b) (4) cleanrooms are installed of HEPA filters. Air flow is cascaded out from (b) (4)

classification areas. The pressure differential is (b) (4) and the air change rate is(b) (4) changes per hour for the Grade (b) (4) cleanrooms. The manufacturing areas are controlled of temperature at (b) (4) °C in production mode. No humidity control in the manufacture room. Both differential pressure and temperature are monitored via a qualified software system. Alarm sounds and warning lamps are physically located (b) (4) of the cleanroom areas. The alarm systems are tested on an (b) (4) basis. The HVAC system is qualified through initial IQ/OQ/PQ and requalified (b) (4) through calibration, maintenance, and periodic review per Validation Master Plan at Novavax.

Environmental Monitoring in the Grade (b) (4) manufacturing rooms (b) (4) includes (b) (4) microbial sampling and (b) (4) non-viable particulate sampling with the predefined acceptance criteria aligning with (b) (4) .

Product contact equipment in Novavax AB is either single-use or dedicated. Single-use equipment includes (b) (4) Dedicated equipment includes (b) (4) The Matrix (-A or -C) manufacturing is performed in all (b) (4) manufacturing lines. IQ/OQ/PQ was performed for each manufacturing line, including the (b) (4) Systems with associated (b) (4) located in manufacturing rooms (b) (4) . Periodic review of equipment qualification status is performed per internal procedures.

Cleaning of the dedicated equipment includes the following:

- Manual cleaning using (b) (4) for (b) (4)
- The (b) (4) systems with respective (b) (4) are (b) (4) after cleaning.

Cleaning validation for the (b) (4)

Disinfectants used in facility cleaning include (b) (4) . Disinfectant Efficacy Study was performed using representative (b) (4) and challenged using in-house microbial isolates and mold. Testing results in the DES study met the acceptance criteria (*i.e.*,(b) (4) of Gram positive/negative microorganisms and (b) (4) of bacterial spores and molds for each disinfect at specified contact times). Routine cleaning of cleanrooms includes (b) (4) using(b) (4) and (b) (4) is used when introducing equipment into the cleanrooms when necessary.

Utility systems used in NVX AB for Matrix (-A or -C) manufacture include compressed air and WFI system:

- Compressed air is generated on-site from a qualified system. (b) (4) maintenance and sampling are performed to verify the function of the compressed air generation system.
- WFI for manufacturing processes (*i.e.*, (b) (4) are purchased. Purchased WFI is tested of sterility per vendor's CoA. Novavax AB also has a WFI generation system (b) (4) . Chemical and microbial sampling per (b) (4) standards is routinely performed on the WFI system. Purified water generated on-site is used for the preparation of (b) (4)

Contamination prevention and cross-contamination control procedures in NVX AB include the following:

- The manufacturing area in NVX AB is solely used to produce the Matrix adjuvant and adjuvant components. No other types of products are manufactured in NVX AB.
- The GMP manufacturing area is segregated and controlled via area classifications, and access controls (via personnel airlocks and material airlocks) and flows of material, equipment, personnel, products, and wastes.
- Dedicated AHU (b) (4) is used for the Matrix (-A or -C) production area.
- Equipment is dedicated.
- Line clearance is performed by (b) (4) operators between (b) (4) batches per internal procedure.

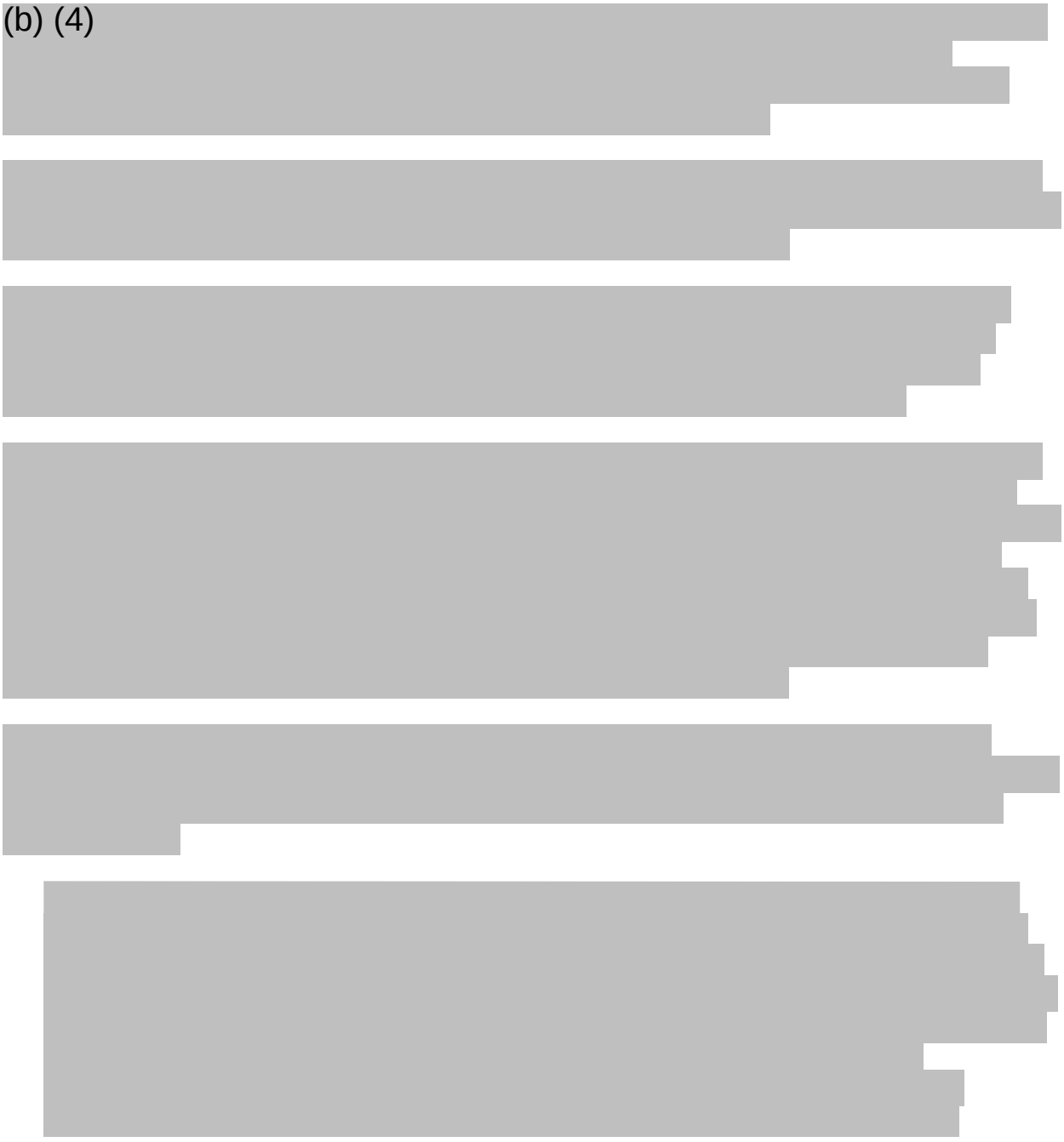
At release, Matrix (-A or -C) is controlled of microbiological attributes as follows:

- (b) (4)

Reviewer's Comments: *NVX-AB is a starting-material manufacturing facility to the Novavax COVID19 Vaccine manufacturing process. In the* (b) (4) *DP manufacturing site (SIIPL), Matrix-A and Matrix-C are mixed to generate Maxtrix-M1, and after Matrix-M1 addition, the co-formulated DP is sterile filtered prior to aseptic filling. The facility and equipment information provided from NVX AB, the manufacturer the Matrix-A and Matrix-C manufacturing site* (b) (4) *scales), appears acceptable, and the risk of Matrix (-A or -C) manufacture appears to be relatively low in terms of sterility assurance for the final drug product as equipment and production areas are dedicated to Matrix manufacturing, tight bioburden and endotoxin specs are established, cleanrooms are maintained with line clearances performed, facility disinfectants are qualified, equipment cleaning is validated, and qualified WFI is used for preparation of* (b) (4) *.*

4 pages determined to be not releasable: (b)(4)

(b) (4)



3.2.R REGIONAL INFORMATION [SIIPL]

This section of the review memo covered the following submissions:

- 3.2.R.1 Device: PFS *for JN.1 strain* (STN 125817/0.44)
- 3.2.R.2 PFS Technical Documents *for JN.1 strain* (STN 125817/0.44)

The device information provided for the off-the-shelf (b) (4) syringe (primary container closure system) remains the same as previously submitted to EUA 28237/0.246.

Reviewer's Comments: *Control and compliance of the PFS device to JN.1 vaccine production were reviewed and found acceptable during authorization of EUA 28237/0.246 (August 30, 2024) and are consistent with information in the BLA.*